

2415F USA

Via Telefax

AMENDMENTS TO THE SPECIFICATION:

Please add the following abstract, a copy of which is provided on a separate sheet:

ABSTRACT OF THE DISCLOSURE:

Methods of treating osteochondral lesions by the intraarticular application of a mixture of sodium hyaluronate and chondroitin sulfate are disclosed.

Please delete the numerical reference in the lower left hand corner of each page of the specification.

Please amend the paragraph beginning on Page 1, line 13 to read as follows:

At The main objective of the invention is to introduce the new medical use of the mixture of sodium hyaluronate and sodium chondroitin sulfate for the regeneration of damaged articular cartilage, caused during osteoarthritis, treatment methods and the provision of the components for such therapies, as well as their protection of such cartilage.

2415F USA

Via Telefax

*Please amend the paragraph beginning on page 2, line 9  
to read as follows:*

Ar | The clinical manifestations of the development of the condition are: increased volume of the joint, pain, crepitation and functional disability that, gradually and steadily, first hinders the performance of lengthy walks and forced flexion and extension movements, depending on the affected joint, and then pain and limitation of minimum efforts emerge as well as pain at rest which interrupts sleeping+. ~~if~~ If the condition persists without correction and/or therapy, the joint is totally destroyed, leading the patient to major replacement surgery with total prosthesis, or to disability.

*Please amend the paragraph beginning on page 2, line 22  
to read as follows:*

Ar | a) The application of tendinous, periosteal, fascial, muscular or perichondral grafts.

*Please amend the paragraph beginning on page 3, line 1  
to read as follows:*

Ar | b) The implantation of fibrin or cultured chondrocytes. (Osteochondral Grafts Improve Symptoms but May Increase Risk- Of Osteoarthritis. [medscape.com/con/2000/AAOS/story.cfm](http://medscape.com/con/2000/AAOS/story.cfm)).

2415F USA

Via Telefax

Please amend the paragraph beginning on page 3, line 6 to read as follows:

- Cb 1
- d) Implantation of synthetic ~~matrices~~ matrices, such as collagen, carbon fiber.

Please amend the paragraph beginning on page 3, line 17 and ending on page 4, line 2 to read as follows:

Cu

The treatment that has 74% to 90% effectiveness and produces excellent results, similar to that presented in this invention, is the transplantation of cultured autologous chondrocytes, a treatment started in 1987 in Sweden and in 1995 in the USA, ~~that it~~ It consists of taking chondral cellular material from the patient, and sending it to a laboratory where it is seeded in a proper medium for its proliferation, and, once enough volume is achieved after a variable period that may last from weeks to months, ~~it transported~~ transporting it in a special container and ~~implanted~~ implanting it in the damaged tissues, to covering ~~cover~~ the tissue's defects. This is an expensive procedure that requires the patient to be in the operating room for the removal of the necessary cellular material, and subsequently for the implantation of the proliferated material. ~~Furthermore~~, a waiting period is needed for the implant to be ready. (VLADIMIR, Bobic, MD AAOS Annual Meeting, March 16, 2000.)

2415F USA

Via Telefax

**Please amend the paragraph beginning on page 4, line 3  
read as follows:**

Gr A recent treatment, currently in vogue, is the intraarticular ~~application~~ instillation of Hylan G-F 20 (Synvisc, Hyalgan, Artz etc.), ~~a one of the~~ modified form of one of the substances contained in the product used in this invention. This substance only acts on the rheologism of the synovial fluid, producing an almost immediate sensation of free movement and a marked reduction of pain; however, its effect is temporary because that element remains within the articular chamber for only 72 hours before it is absorbed and metabolized. The residual effects of this substance act on the synovial receptors causing a pain reduction that lasts several weeks and even months. However, this isolated effect is counterproductive for the course of the disease and for the viability of the cartilage because, as it masks the symptoms, the joint is used with more intensity and its destruction is accelerated as the original problem is not corrected and the the damaged articular cartilage is not restored.

2415F USA

Via Telefax

**Please amend the paragraph beginning on page 4, line 16 to read as follows:**

As an antecedent to this invention, in 1982, the applicant began applying sodium hyaluronate (SH) to thoroughbred race horses in his stable at Hipódromo de las Américas (Las Américas Race Track), in Mexico City, because the knees and ankles are the most commonly injured joints in these horses. Veterinarians at racetracks in the USA had already used this procedure, observing the beneficial reaction that this compound produced in the injured knees of the horses. ~~the~~ The applicant considered its use in humans, ~~added to~~ with the addition of some substance to cause the restoration of the damaged surface.

**Please amend the paragraph beginning on page 5, line 1 to read as follows:**

In 1996 while visiting Alcon Laboratories in Mexico City, the applicant found out that one of the company's ophthalmologic products contained both above mentioned substances in a gel suspension (VISCOAT). The inventor obtained detailed information, including the product monograph that states that ~~is~~ it has no reported side effects in intraocular use; furthermore, there are ample references from efficacy and safety studies of this product (CILCO, In, Summary of safety and efficacy for Viscoat, 1984). It was then that the applicant decided to use it in patients with osteoarthritis disorders of all degrees, and subsequently perform [a discrimination] an analysis.

2415F USA

Via Telefax

*Please amend the paragraph beginning on page 5, line 10 to read as follows:*

G10  
The above mentioned usual treatments include antiinflammatories, antirheumatics, systemics, physiotherapy, infiltration of depot steroids and, recently, viscoprotection has emerged. It includes substances such as high molecular weight hyaluronic acid (Hylan G F 20) which is ~~infiltrated~~ instilled in the joint and reduces the painful symptoms.

*Please amend the paragraph beginning on page 5, line 15 to read as follows:*

A11  
It has been proven that the change of the intraarticular fluids produces a blockage of the nociceptors of subsynovial and capsular tissues and that, in addition to the mechanical factors of the osteochondral pathology, the fluids exert a relevant influence with their lubricating properties. Thus the change in viscosity of these fluids acts favorably on the painful osteochondral symptoms when sodium hyaluronate is ~~infiltrated~~ instilled.

*Please amend the paragraph beginning on page 6, line 8 to read as follows:*

A12  
With this matrix, the symptomatic evolution is significantly favorable and long lasting due to the regeneration of chondral lesions and no side effects have been reported except in a patient who reported pain and a slight increase in volume at the site of application, which ~~yielded~~ subsided spontaneously in 24 hours; he was only given acetaminophen as an analgesic.

2415F USA

Via Telefax

Please amend the paragraph beginning on page 8, line 14 to read as follows:

It is presented under the trade name of VISCOAT<sup>®</sup>(+), it is prescribed for the treatment of chondral lesions in Osteoarthritis (OA) in patients who fail to respond adequately to traditional non-drug therapies and to plain analgesics.

Please amend the paragraph beginning on page 8, line 17 to read as follows:

It is protected under US ~~patent number No 4-486~~ 416Patent No. 4,486,416 and it is also registered before the SSA (Mexican Health Secretariat) under registration number Reg SSA Mex. No. 0735 C 88.

Please amend the paragraph beginning on page 13, line 3 to read as follows:

A visual analog clinical scale (SCRIPPS CLINIC FOR SPECIAL SURGERY) was applied and 309 knees (95.07%) showed immediate significant improvement and satisfactory evolution for up to two years of follow-up, 250 knees (83.3%) remained in the same good conditions without needing to take any NSAID for up to 50 months of follow up, 32 knees (13%) showed moderate pain and 18 cases (6%) showed no short and medium term improvement. Finally, from 16 grades I, II, III and IV osteoarthritis coxofemoral joints (hip), 14 grade I and II coxofemoral joints showed excellent results, and 2 of these grade III and IV coxofemoral joints, due to the advanced

2415F USA

Via Telefax

915 | degree of deterioration=, did not obtain any positive results.

---